DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

DEC 2 9 2000

Our STN: BL 103772/1007 (Replaces Ref. No. 99-1234)

Martin Page
Centocor, Inc.
200 Great Valley Parkway
Malvern, PA 19355

Dear Mr. Page:

Your request to supplement your biologics license application for infliximab (Remicade®) to expand the indication to include the inhibition of progression of structural damage in patients with rheumatoid arthritis who have had an inadequate response to methotrexate has been approved.

We acknowledge your agreement to provide additional information on the safety and efficacy of infliximab in combination with methotrexate and to conduct post-marketing studies as described in your commitment letters of December 11, December 18, and December 20, 2000, as outlined below:

1. To further study the safety and efficacy of infliximab in a randomized, placebo-controlled study of 1000 patients with rheumatoid arthritis who are to be treated initially with either 3mg/kg or 10mg/kg of infliximab in combination with methotrexate. This study will include patients who are treated with multiple disease-modifying anti-rheumatic drugs, and will focus upon the effects of infliximab on the development of infections. Patients initially receiving the lower dose of infliximab will be given higher doses if they do not respond to treatment. The protocol will be submitted for CBER review by January 31, 2001 and finalized by April 30, 2001. The study will be initiated by September 30, 2001 and accrual will be completed by September 30, 2002. A final study report will be submitted by September 30, 2004.

2. To collect additional infectious, autoimmune, and neoplastic adverse event data in patients receiving up to 10 mg/kg of infliximab every 4 or 8 weeks in combination with methotrexate. Data regarding tuberculosis and malignancies will be submitted to CBER within 20 days of initial receipt of the information while data on other adverse events will be submitted quarterly. In addition to the safety data collected from patients in the randomized clinical trial described in item 1 above, you will also collect safety data from the following:

a. Two registries that will each enroll 5000 patients; one for patients with rheumatoid arthritis and the other for patients with Crohn's disease. These registries will complete enrollment within the next 12 to 18 months.

b. Six ongoing or planned Centocor-sponsored trials that involve treatment of patients with infliximab for at least one year in duration.

3. To continue long-term safety follow-up of patients who participated in the earlier conducted studies of infliximab and provide this information to CBER on a periodic basis, at least annually. Patients will be followed for a period of at least five years following the last infusion of infliximab.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

This information will be included in your biologics license application file.

Sincerely yours,

Karen D. Weiss, M.D.
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research